EXHIBIT Q

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Inhibition of angiogenesis and metastases of the Lewis-lung cell carcinoma by the quinoline-3-carboxamide, Linomide.

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Linomide has antitumor effects when administered in vivo but not in vitro. Recent data indicate that at least part of this effect can be attributed to anti-angiogenic properties. The aim of the present investigation was to study the anti-angiogenic effects of Linomide on early tumor-induced angiogenesis in vivo, using a newly developed skinfold chamber technique in the mouse, and to relate this to the effect of Linomide on the number of metastases that develop from a s.c. implanted tumor. Tumor spheroids of Lewis lung cell carcinoma (LLC) with a diameter of about 800 microns were implanted in dorsal skinfold chambers inserted on CB6/F1 mice. Tumor cells were pre-labelled with a fluorescent vital dye (CMTMR), which allowed the estimation of the growth of the implanted tumor spheroids. Linomide, given orally from day 7 to day 11, reduced the incidence of lung metastasis arising from LLC tumors at day 21 in a dose-dependent manner, a 55% reduction being found at a dose of 50 mg/kg/day (N = 19 for the controls and N = 10 for treatment groups). In the dorsal skinfold chamber, the vascular network in Linomide treated animals (100 mg/kg/day, N = 22) was more heterogenous, large areas within the tumor being completely avascular; in addition, capillary density at the tumor site was reduced by 34% 6 days after implantation and by 39% after 14 days. In the control group (N = 16), tumor volume doubling time was not significantly different in the early avascular part of the observation period as compared to the later vascular phase; this indicates that the growth of these micro-tumors in the early avascular phase is not angiogenesis dependent. However, in the Linomide treated animals, tumor volume doubling time was significantly prolonged by 42% during the later part of the observation period. Taken together, the data indicate that the prolongation of the tumor doubling time is due to the anti-angiogenic activity of Linomide.